UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/007,331	11/09/2001	James C. Paulson	019957-011211US	3312

20350 7590 04/21/2005

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
PROUTY, REBECCA E	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 04/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/007,331	PAULSON ET AL.	
	Examiner	Art Unit	
	Rebecca E. Prouty	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57,59,61-65,67-70,101 and 112* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57, 59, 61-65, 67-70, 101 and 112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/1/05 has been entered.

Claims 1-56, 58, 60, 66, 71-100 and 102-111 been canceled. Claims 57, 59, 61-65, 67-70, 101 and 112 are still at issue and are present for examination.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 57, 59, 61-65, 67-70, 101, and 112 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined disclosures of Bergh et al (US Patent 5,272,066), Maras et al (US Patent 5,834,251), Weinstein et al. (JBC 257: 13845) and Williams et al. (Glycoconjugate J. 12: 255).

Each of Bergh et al. and Maras et al. teach methods of *in vitro* enzymatic modification of glycoproteins, particularly natural and recombinant glycoproteins intended for therapeutic applications. Each of Bergh et al. and Maras et al. teach that such modifications improve the circulatory half-life of the glycoproteins as well as providing other benefits as well. (see particularly columns 1-3 of Maras et al. and column 5 or Bergh et al.). Maras et al. teach that the glycoprotein of interest is preferably an immunoglobulin (see column 16, lines 44-46). These methods comprise incubating a glycoprotein either having or having been modified to have a terminal galactose residue in a Galβ1→4GlcNAc or a Galβ1→3GlcNAc linkage with a sialyltransferase and a sialic acid donor. Bergh et al. teach the use specifically of the bovine colostrum or rat liver Galβ1→4GlcNAc α2→6 sialyltransferase (i.e., ST6Gal I) and rat liver Galβ1→3(4)GlcNAc α2→3 sialyltransferase (i.e., ST3Gal III). Maras et al. teach the use specifically of the rat liver

Galβ1→4GlcNAc α2→6 sialyltransferase (i.e., ST6Gal I). Maras et al. further teach that as a result of the described methods, that large-scale stereo-controlled oligosaccharide synthesis will be possible (see column 28, lines 52-67). Neither Bergh et al. nor Maras specifically show a commercial-scale method nor do they discuss the extent of sialylation achieved in their methods.

Weinstein et al. teach the enzymatic properties of the sialyltransferases (i.e., rat liver ST6Gal I and ST3Gal III used in the methods taught by Bergh et al. and Maras et al. Weinstein et al. further teach conditions under which each of these enzymes can fully sialylate all available substrate (see Table 4).

Williams teach the large scale recombinant expression and kinetic properties of the sialyltransferases (i.e., rat liver ST6Gal I and ST3Gal III used in the methods taught by Bergh et al. and Maras et al.

Therefore it would have been obvious to one of skill in the art to use the recombinant enzymes provided by Williams to scale up the methods taught by Bergh et al. and Maras to a commercial scale for the production of therapeutic glycoproteins. One would have had a reasonable expectation of successful scale-up in view of the explicit statement of Maras et al of such

expectation and in view of the availability of large quantities of enzyme from recombinant production as taught by Williams. Furthermore, one of skill in the art would have reasonably expected to be able to achieve virtually complete sialylation of all available substrate galactose residues in view of the teaching of Weinstein et al.

Applicants argue that the examiner has not pointed to any specific teaching of large scale production of modified glycoproteins in the cited art and that the examiner has not provided any evidence to show why one of skill would reasonably expect that 80% sialylation rates could be achieved at the commercial scale. This is not persuasive because the primary references clearly suggest scale up of the reactions taught to a commercial scale for all the reasons previously discussed. Furthermore, while the primary references do not discuss high sialylation rates as recited in the claims, Weinstein et al. clearly teach conditions in a 60 µl reaction in which this level can be achieved. How one scales up a reaction is well known in the art. There is no reason to believe a skilled artisan could not scale up these reactions to commercial scale as scale up is simply a mathematical calculation. While scale up to commercial scale might require amounts of enzyme or other reactants which are economically excessively costly, there is no reason that a

skilled artisan would expect the scaled up reaction to act substantially differently. A prima facie showing of obviousness does not require a showing that the claimed method can be done cost-effectively. Furthermore, even if minor differences were observed, one of skill in the art would reasonably expect to be able to adjust the scaled up reaction using techniques well known in the art, as a skilled artisan would reasonably expect that most differences would be a result of the increased volume such that controls to ensure adequate mixing, constant temperature and pH, adequate aeration, etc. would be used.

Applicant state that in the Final Rejection the examiner acknowledged that the evidence of record shows commercial success of the invention. This statement is not accurate. The examiner acknowledged that the declaration provides **some** evidence of commercial success. Acknowledgement of some evidence is not an acknowledgment of a complete demonstration of commercial success. As such the issues with regard to applicants declarations is not just whether there is a nexus between the success and the claimed invention but whether commercial success has been demonstrated **and** if so is there an nexus. The only statements in the previous declaration which relate to commercial success itself is point 6) of the declaration which states "In my capacity as Vice President of

New Product Development of Neose, I have directly participated in negotiating agreements with more than 20 companies to assess the feasibility of the technology for in vitro sialylation of recombinant therapeutic glycoproteins in development. All feasibility studies completed to date have been successful. Many of these successful feasibility studies have led to ongoing negotiations for commercial licenses to the technology for large-scale manufacture of human glycoprotein therapeutics. In addition, the present technology is being employed as an essential part of ongoing collaborative research and development agreements with other companies to develop commercial manufacturing methods for cancer vaccines and treatments for neurological diseases". The evidence does not show that the "feasibility studies" were conducted at commercial scale as recited in the claims and thus the relationship of these studies to the claimed invention which is clearly limited to commercial scale reactions is not clear. Furthermore, it is not clear how many of the successful feasibility studies actually led to commercial licenses, nor how many commercial licenses would constitute "commercial success". As such a conclusion that the declaration unequivocally shows commercial success is clearly premature. Furthermore, even assuming that the evidence presented does show commercial success, applicants have clearly

not sufficiently established a nexus between the commercial success and the instantly claimed invention. As stated in the Advisory Action of 12/29/04, the burden of establishing nexus clearly falls on applicants. Furthermore, as the specification clearly establishes the importance of the amounts of enzyme required in a commercial scale reaction as a highly important variable in the cost of the method, and the instant claims lack any limitations with regard to this variable applicants clearly have not established that any commercial success that has been demonstrated was not highly dependent on this. As stated in MPEP 716,03(a) "In order to be commensurate in scope with the claims, the commercial success must be due to claimed features, and not to unclaimed features". Page 11, lines 4-10 of the specification states "The substrate specificity of the sialyltransferases is only the first criterion an enzyme must satisfy for establishing a method for sialylation of commercially important recombinant or transgenic glycoproteins. The sialyltransferase must also be able to effect sialylation efficiently and completely for a variety of glycoproteins, and support the scale-up to the 1-10 kg of recombinant glycoprotein with relatively low cost and infrastructure requirements." and page 23, lines 2-6 state "Sialyltransferases capable of sialylating glycoproteins to a level of at least 80% using no

more than 50 munits/mg of acceptor are considered "practical" for use in commercial-scale glycoprotein modification. The analysis utilizes assay conditions that are practical for use on a large scale, e.g., 1-10 mg/ml glycoprotein acceptor and a sialyltransferase concentration of (2-50 munit/mg of acceptor)". Other portions of the specification (i.e., page 11, line 24 - page 12 line 2, and page 18, line 12 - page 20) also establish the amount of enzyme necessary as an essential variable in the cost of the method and thus a variable virtually certain to be involved in any decision to license the technology. However, applicants claims are not limited to methods of sialylation which produce greater than 80% sialylation at an enzyme concentration of no more than 50 munits/mg of acceptor and the evidence of record (including both Dr. Zopf's previous declaration as well as the second declaration presented with the current response) provides no evidence to suggest that this unclaimed limitation was not at least in part a factor in any commercial success. In fact it appears that in the only commercial scale sialylation reaction documented within either declaration (i.e., the Thomas et al. article), that the levels of enzyme used were no more than 50 munits/mg of acceptor suggesting that this variable may well have been a highly important factor in any decision.

Applicants submitted a second declaration by Dr. Zopf to further address the issue of nexus of the claimed invention and the commercial success. This declaration has been considered but is not persuasive to overcome the rejection. While the declaration states "In our experience, producers of recombinant therapeutic proteins have been interested in the claimed *in vitro* methods because the methods can be used to improve glycosylation without altering the host cells or culture conditions that have been optimized for other purposes, such as yield. In addition, the methods can be used in combination with in any expression system, such as bacteria yeast, fungi, or plants. Prior to the advent of the claimed technology, producers of recombinant therapeutic glycoproteins had no commercially feasible means for achieving this goal.", there is no evidence to back up this opinion as to the motivation of others and absolutely no evidence that other factors were not also decisive in any actual decision as to whether to adopt the claimed methods or use other art methods of producing a product with the desired glycosylation patterns. Furthermore, it should be noted that statement 5 (i.e., "As explained at page 11 and illustrated in Figure 3, none of the currently used recombinant expression systems produce proteins having glycosylation as found in human cells") of the declaration is factually incorrect. Human cell

expression systems such as kidney 293 cells or HeLa cells are well known in the art and clearly do produce glycosylation as found in human cells since they are human cells. While it is clear from the specification and the declarations submitted that the claimed *in vitro* method would have some advantages over engineering of the recombinant host to alter the glycosylation patterns, it is also clear that it would have some disadvantages also (i.e., additional cost associated with an additional process step including the cost of all enzymes and sugar donors as well as additional time and labor for the additional step, potential purification issues with regard to the removal of the components of the *in vitro* method, potential issues of degradation of the desired protein during the additional processing step etc.). The ultimate decision as to which approach to use would likely be based on as assessment of whether the gains in amount of useful product produced were significant enough to balance the additional costs and potential disadvantages of the *in vitro* method. Therefore, the costs involved in the amount of enzyme used would likely be significant and thus unclaimed limitations are likely to have been a significant factor in any commercial success that has been derived from the instant invention.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 57, 59, 61-65, 67-70, 101, and 112 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 57, 59-64, 66-69 and 82 of U.S. Patent No. 6,399,363. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the

conflicting claims are not identical, they are not patentably distinct from each other because claims 57, 59, 61-65, 67-70, 101, and 112 are generic to all that is recited in claims 57, 59-64, 66-69 and 82 of U.S. Patent No. 6,399,363. That is, claims 57, 59-64, 66-69 and 82 of U.S. Patent No. 6,399,363 fall entirely within the scope of claims 57, 59, 61-65, 67-70, 101, and 112 herein or, in other words, claims 57, 59, 61-65, 67-70, 101, and 112 are anticipated by claims 57, 59-64, 66-69 and 82 of U.S. Patent No. 6,399,363. Specifically, the claims differ only in that all of the claims of U.S. Patent No. 6,399,363 include limitations that greater than 80% of the available terminal galactose residues are sialylated and that the sialyltransferase is present at a concentration of 50 mU/mg of glycoprotein or less. As such the claims of the previous patent clearly anticipate the instant claims.

Applicants did not address the instant rejection in the current response. As such the rejection is maintained for the reasons of record.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca E. Prouty whose telephone number is 571-272-0937. The examiner can normally be reached on Tuesday-Friday from 8 AM to 5 PM. The examiner can also be reached on alternate Mondays

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura

Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rebecca Prouty
Primary Examiner
Art Unit 1652